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Visible-light-promoted *S*-trifluoromethylation of thiophenols with trifluoromethyl phenyl sulfone†

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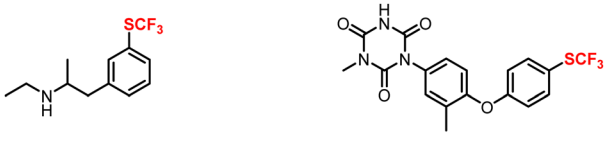
Trifluoromethyl phenyl sulfone is traditionally a nucleophilic trifluoromethylating agent. Herein, we report the first example of the use of trifluoromethyl phenyl sulfone as a trifluoromethyl radical precursor. Arylthiolate anions can form electron donor–acceptor (EDA) complexes with trifluoromethyl phenyl sulfone, which can undergo an intramolecular single electron transfer (SET) reaction under visible light irradiation, thus realizing the *S*-trifluoromethylation of thiophenols under photoredox catalyst-free conditions. Similar *S*-perfluoroethylation and *S*-perfluoro-*iso*-propylation of thiophenols are also achieved using the corresponding perfluoroalkyl phenyl sulfones.

The trifluoromethylthio (CF_3S) group has been often incorporated into organic molecules to enhance the lipophilicity,[1] thus improving their ability to cross lipid membranes and their *in vivo* absorption rate.[2] In addition, given the electron-withdrawing property of the CF_3S group, trifluoromethylthiolated compounds usually have higher stability (compared with their non-fluorinated counterparts) under acidic environments.[3] As a result, CF_3S-containing molecules have found many applications in pharmaceuticals, such as the appetite depressant drug Tiflorex and the anticoccidial drug Toltrazuril (Fig. 1).[4] During the past decade, transition metal-catalyzed aromatic trifluoromethylthiolation[5] and *S*-trifluoromethylation of thiophenols[6] have been developed.

Furthermore, transition-metal-free aromatic trifluoromethylthiolation reactions have emerged;[7] however, they suffer from some disadvantages, such as the requirement of expensive reagents and/or poor compatibility of functional groups.

Fluoroalkyl sulfones, a class of stable and easily accessible organofluorine compounds, have been widely used in selective fluoroalkylation of organic compounds.[8] In 2016, we reported the first example of using fluoroalkyl sulfones as fluoroalkyl radical precursors for efficient fluoroalkylation.[9] Thereafter, we developed a series of radical fluoroalkylation reactions involving fluoroalkyl sulfones.[10] However, in the case of trifluoromethyl sulfone-enabled radical trifluoromethylations, only trifluoromethyl heteroaryl sulfones (with high reduction potentials) were successfully used as trifluoromethyl radical precursors, while the more readily available trifluoromethyl phenyl sulfone ($PhSO_2CF_3$, **2a**; with relatively lower reduction potential) failed.[9,10a,d] To date, **2a** has only been used as a nucleophilic trifluoromethylation reagent (Scheme 1a and b).[11] Following our continuous efforts in developing fluoroalkyl sulfones in organic synthesis, herein, we report the first case of using **2a** as a trifluoromethyl radical precursor and its application in the trifluoromethylation of thiophenols (Scheme 1c).

Initially, we evaluated the reactivity of $PhSO_2CF_3$ (**2a**) in the *S*-trifluoromethylation of thiophenol (**1′**) in DMF solution under dark conditions at room temperature. Although the thiophenolate anion was known to possess good reducing ability,[12] it could not reduce **2a** under dark conditions (Table 1, entry 1). So we carried out the reaction under the irradiation of blue LEDs. To our delight, the yield reached 61% after 12 hours (Table 1, entry 2). Further screening of the solvents showed that the reaction only worked in highly polar solvents (Table 1, entries 2–7), and the yield increased to 72% in DMAc (Table 1, entry 3) or NMP (Table 1, entry 5). During the screening of bases (Table 1, entries 3 and 8–11), it was found that when Cs_2CO_3 was used, the reaction gave the highest yield (Table 1, entry 3). It is likely that Cs_2CO_3 has both good basicity



Tiflorex *Toltrazuril*

Fig. 1 Examples of SCF_3-containing drugs.

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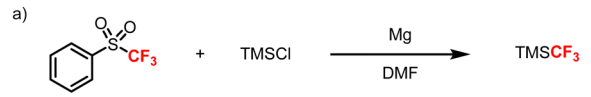
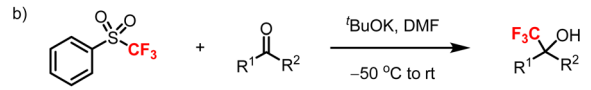
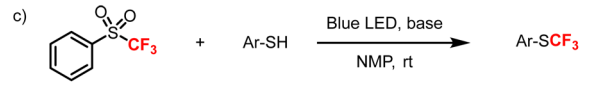
Previous work: Trifluoromethyl phenyl sulfone as a trifluoromethyl anion precursor



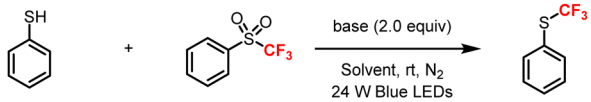


***This work**: Trifluoromethyl phenyl sulfone as a trifluoromethyl radical precursor*



Scheme 1 Trifluoromethylations with trifluoromethyl phenyl sulfone.

Table 1 Survey of reaction conditions for trifluoromethylation of thiophenol[a]



1' 2a 3'

Entry	Solvent	Time (h)	Base	Yield[b] (%)
1[c]	DMF	12	Cs_2CO_3	Trace
2	DMF	12	Cs_2CO_3	61
3	DMAc	12	Cs_2CO_3	72
4	DMSO	12	Cs_2CO_3	33
5	NMP	12	Cs_2CO_3	72
6	DMPU	12	Cs_2CO_3	52
7	CH_3CN	12	Cs_2CO_3	3
8	DMAc	12	K_3PO_4	64
9	DMAc	12	K_2CO_3	54
10	DMAc	12	Na_2CO_3	58
11	DMAc	12	NaH	61
12	DMAc	18	Cs_2CO_3	72
13	NMP	18	Cs_2CO_3	80
14	NMP	24	Cs_2CO_3	81
15[d]	**NMP**	**24**	**Cs_2CO_3**	**81**
16[e]	NMP	24	Cs_2CO_3	72

[a] Reaction conditions: **1'** (0.5 mmol, 1.0 equiv.), **2a** (0.6 mmol, 1.2 equiv.), and solvent (5.0 mL). [b] Determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard. [c] Under a dark environment. [d] **2a** (0.55 mmol, 1.1 equiv.). [e] Under white light irradiation.

and good solubility, so it is able to efficiently promote the occurrence of single electron transfer reduction in our reaction. When the reaction time was elongated to 18 hours, the yield did not increase when DMAc (Table 1, entry 12) was used as a solvent; however, the yield increased to 80% in NMP after 18 hours (Table 1, entry 13), and increased to 81% when the reaction time was 24 hours (Table 1, entry 14). When the amount of **2a** was reduced from 1.2 equivalents to 1.1 equivalents, the yield kept the same (Table 1, entry 15). It is worth mentioning that the yield of the reaction was 72% under white light irradiation (Table 1, entry 16).

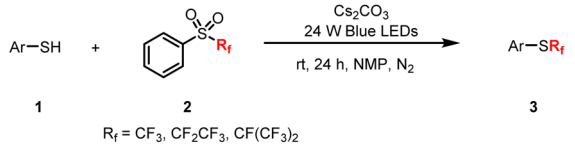
With the standard reaction conditions in hand (Table 1, entry 15), we examined the substrate scope of this *S*-perfluoroalkylation protocol. As shown in Table 2, the reaction was sensitive to the electronic nature of thiophenols **1**. For electron-rich substrates, the yields were moderate with reagent **2a**, but the yields could rise by using 1-(trifluoromethyl)-4-((trifluoromethyl)sulfonyl)benzene (in the cases of **3b** and **3c**). For electron-neutral substrates (**1a**, **1d** and **1g**) and electron-deficient substrates (**1h–1o**), the yields were mostly good to excellent. This reaction was also amenable to thiophenols with steric hindrance (such as **1e**). Furthermore, thiophenols bearing *tert*-butyl (**1b**), methoxy (**1c**), amide (**1f**), methylthio (**1g**), ester (**1h** and **1i**), carboxylic acid (**1j–1l**), cyano (**1m**), carbonyl (**1n**), and sulfonyl (**1o**) were all applicable in this reaction. This fluoroalkyl sulfone-enabled radical fluoroalkylation reaction proceeds smoothly with substrates bearing a range of heterocyclic motifs, including pyridine (**1p**), pyrimidine (**1q** and **1r**), and benzothiazole (**1s**). The nitro-containing substrate (**1t**), which is often incompatible with the single electron transfer reduction, was also found to give the corresponding product **3t** in 36% yield.

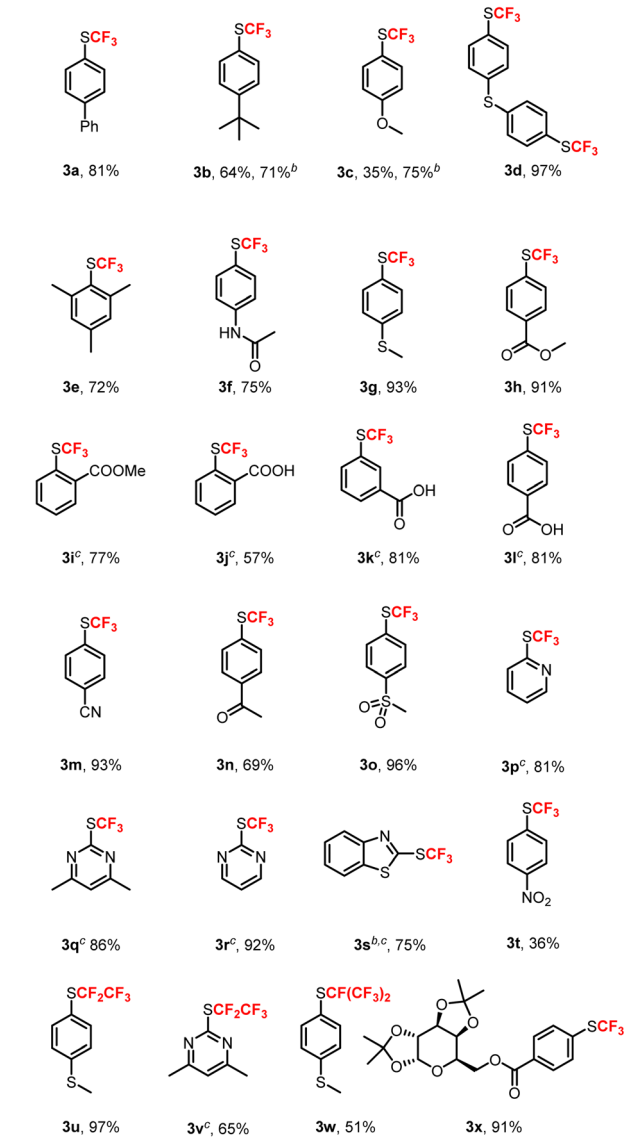
Pentafluorothio (C_2F_5S)-containing compounds are useful in pharmaceuticals and agrochemicals,13 but there are few synthetic methods of pentafluoroethyl aryl sulfide.[14] We found that, in addition to *S*-trifluoromethylation, our synthetic protocol is also suitable for *S*-pentafluoroethylation (**3u** and **3v**) and *S*-perfluoroisopropylation (see **3w**). This *S*-trifluoromethylation method also worked well for a complex molecule (**1x**), and the desired product **3x** was obtained in excellent yield (91%).

Trifluoromethyl heteroaryl sulfones are valuable compounds for organic synthesis.[9,10a,d,15] By using our *S*-trifluoromehtylation method with $PhSO_2CF_3$ (**2a**), we were able to prepare several trifluoromethyl heteroaryl sulfones **4a–4c** (Scheme 2; *S*-trifluoromethylation followed by oxidation) in gram scales (for details, see ESI†).

To gain mechanistic insights into this reaction, a series of mechanistic experiments were performed. Firstly, the reduction potential of $PhSO_2CF_3$ (**2a**) in DMAc was found to be −1.88 V (*vs.* Ag/AgCl), while after adding one equivalent of sodium thiophenolate (PhSNa), the reduction potential of $PhSO_2CF_3$ decreased to −2.21 V (*vs.* Ag/AgCl) (see ESI†). These results suggest that there is a strong interaction between $PhSO_2CF_3$ and PhSNa. Furthermore, both the DMAc solution of PhSNa and the DMAc solution of $PhSO_2CF_3$ were all almost colorless, but the mixed DMAc solution of PhSNa and $PhSO_2CF_3$ was yellow at the same concentration (Fig. 2). UV/vis absorption spectroscopy showed a bathochromic shift by mixing the DMAc solution of PhSNa with $PhSO_2CF_3$ and there is a strong absorption in the blue light region (Fig. 2), which is in agreement with the fact that the reaction needs blue light irradiation. Finally, a 1 : 1 ratio between PhSNa and **2a** in the form of an EDA complex was established based on the Job's plot with UV/vis absorption experiments, in which the maximum absorption appeared at 50% molar fraction of PhSNa (Fig. 3).[16]

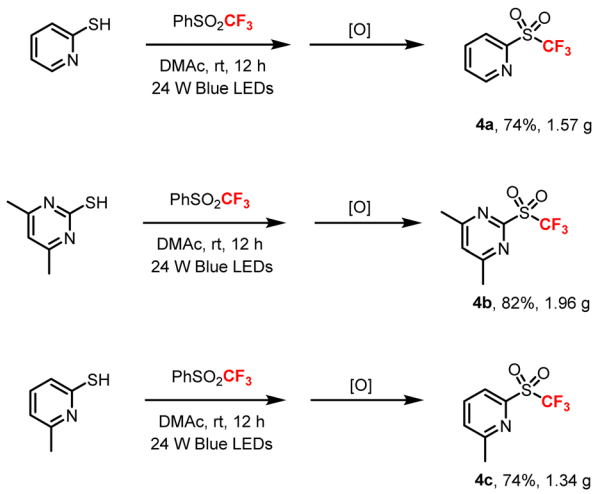
Table 2 Perfluoroalkylation of thiophenols with perfluoroalkyl phenyl sulfones[a]





[a] Reaction conditions: **1** (0.50 mmol, 1.0 equiv.), **2** (0.55 mmol, 1.1 equiv.), Cs_2CO_3 (1.00 mmol, 2.0 equiv.), and NMP (5.0 mL). [b] 4-CF_3-$C_6H_4SO_2CF_3$ was used instead of **2a**. [c] The solvent is DMAc, and the reaction time is 12 h.

Based on the above-mentioned experimental results and the related literature,[17] we propose the following reaction mechanism (Scheme 3). First, thiophenol (PhSH) is deprotonated in the presence of a base, generating a thiophenolate anion (PhS^-). The electron-rich PhS^- interacts with electron-poor $PhSO_2CF_3$ (**2a**) to form the EDA complex (**A**), which can absorb visible light (400–500 nm). Under visible-light irradiation, a single-electron transfer (SET) process occurs from ArS^- to $PhSO_2CF_3$ in the EDA complex, generating a phenylthio radical ($PhS^\bullet$) and a trifluoromethyl phenyl sulfone radical anion (C). Finally, the latter species decomposes to give the desired product and a benzenesulfinate anion (Scheme 3).



Scheme 2 Preparation of trifluoromethyl heteroaryl sulfones.

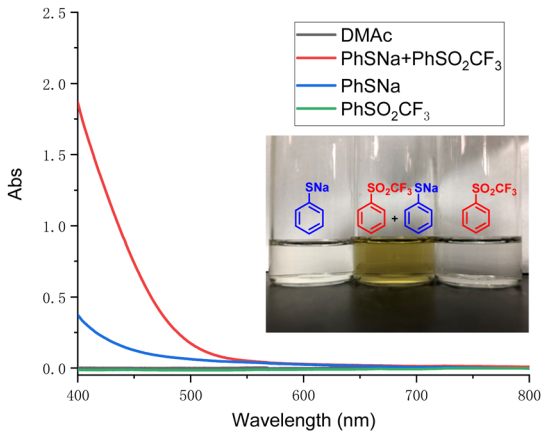


Fig. 2 Maximum absorption wavelengths of different substances in DMAc. The inset shows different colours of the DMAc solutions of PhSNa (left), $PhSO_2CF_3$ and PhSNa (middle), and $PhSO_2CF_3$ (right).

In summary, we have discovered the first case of using trifluoromethyl phenyl sulfone as a trifluoromethyl radical precursor and developed a transition metal-free, photocatalyst-free, and visible-light-promoted *S*-perfluoroalkylation of thiophenols with perfluoroalky phenyl sulfones under mild and straightforward conditions. Further investigation in this direction is underway in our laboratory.

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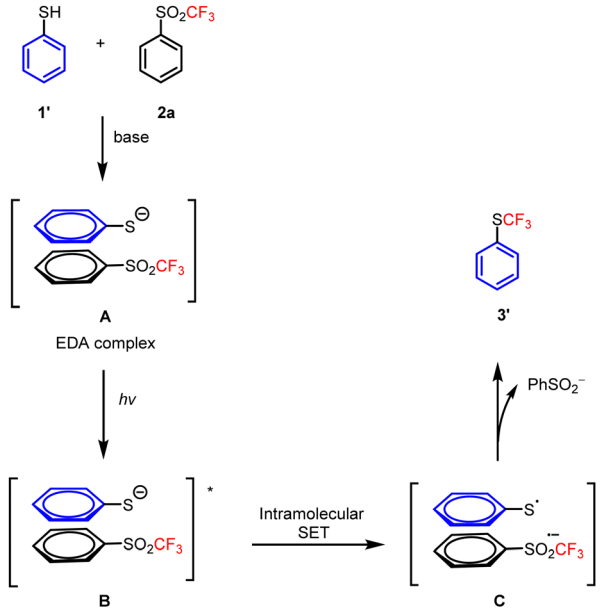

Scheme 3 Proposed reaction mechanism.

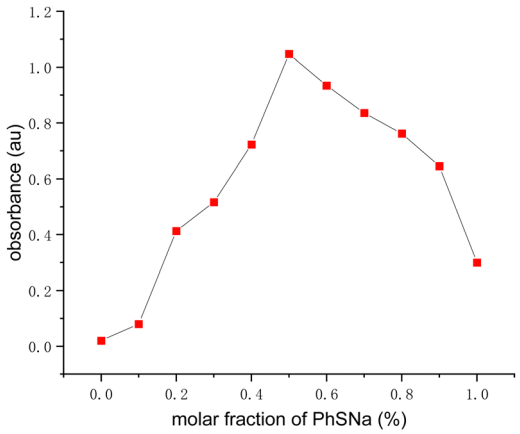

Fig. 3 Job's plot between PhSNa and 2a (measured wavelength: 425 nm) in DMAc.

Conflicts of interest

There are no conflicts to declare.

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